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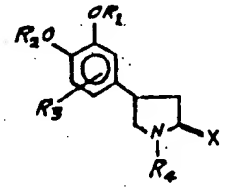
(19)

(54) 4-(ALKOXY-PHENYL)-2-PYRROLIDONES, THEIR PREPARATION AND USE

(71) We, SCHERING AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of Berlin and Bergkamen, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides racemic and optically active 4-(alkoxy-phenyl)-2-pyrrolidones of the general formula I



(I)

in which the groups represented by R_1 and R_2 may be the same or different (except that, when R_4 represents a hydrogen atom and X represents an oxygen atom and R_3 represents a group other than a 2-methoxy or a 6-methoxy group, at least one of R_1 and R_2 represents a group other than a methyl group) and each is a hydrocarbon group which may be unsubstituted or substituted by one or more halogen atoms, hydroxyl groups, cyano groups, carboxyl groups, alkoxy groups, alkoxycarbonyl, carboxamido or substituted or unsubstituted amino groups, or may be a heterocyclic group containing oxygen or sulphur in the ring, or one of R_1, R_2 represents a hydrogen atom and the other represents a hydrocarbon group as specified above, or R_1 and R_2 together represent an alkylene group containing 1 to 3 carbon atoms; R_3 represents a hydrogen atom or a methoxy group; R_4 represents a hydrogen atom or an alkyl, aryl, acyl or carboxamido group; and X represents an oxygen or sulphur atom.

Compounds of the general formula I possess an asymmetrical carbon atom and can therefore exist either as racemates or as individual optical isomers.

Preferably, each of R_1 and R_2 represents a hydrocarbon group as specified, and, advantageously, neither of the groups represented by R_1 and R_2 contains

more than 18 carbon atoms. R_1 and/or R_2 advantageously represents an alkyl group containing 1 to 5 carbon atoms, which may be unsubstituted or substituted as specified.

As hydrocarbon groups R_1 and R_2 there may be mentioned saturated or unsaturated, straight-chain or branched alkyl groups containing 1 to 18 carbon atoms; cycloalkyl and cycloalkyl-alkyl groups preferably containing 3 to 7 carbon atoms in the cycloalkyl moiety; and aryl and aralkyl groups preferably containing 6 to 10 carbon atoms.

Specific alkyl groups which may be mentioned include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, 2-methylbutyl, 2,2-dimethylpropyl, hexyl, heptyl, octyl, nonyl, 1,2-dimethylheptyl, decyl, undecyl, dodecyl and stearyl. Unsaturated alkyl groups may also be considered and R_1, R_2 may represent, for example, vinyl, 1-propenyl, 2-propenyl, 2-propinyl, or 3-methyl-2-propenyl. Alkyl groups, which preferably contain 1 to 5 carbon atoms, may also be mono- or poly-substituted, for example, by halogen, especially fluorine, chlorine and bromine. Examples of halogen substituted alkyl groups are: 2-chlorethyl, 3-chloropropyl, 4-bromobutyl, difluoromethyl, trifluoromethyl, 1,1,2-trifluoro-2-chlorethyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, and 1,1,1,3,3,3-hexafluoro-2-propyl. Other possible substituents in the alkyl groups include, for instance, hydroxyl groups, as, for example, in the case of 2-hydroxymethyl or 3-hydroxypropyl; carboxyl groups as, for example, in the case of carboxymethyl or carboxyethyl; and alkoxy groups in which each alkoxy group preferably contains 1 to 5 carbon atoms as, for example, in the case of methoxymethyl, isopropoxymethyl, 2-methoxyethyl, 2-isopropoxyethyl, 2-butoxyethyl, 2-isobutoxyethyl and 3-pentoxypropyl.

Other substituents which may be incorporated in the groups R_1 and R_2, more especially when R_1 and R_2 represent alkyl groups containing from 1 to 5 carbon atoms, and mainly as terminal substituents, include the following: alkoxycarbonyl groups containing 1 to 5 carbon atoms in the alkoxy residue and carboxyamido groups in which the nitrogen may be mono- or di-substituted by alkyl groups preferably containing 1 to 5 carbon atoms or is a constituent of a 4- to 7-membered ring. Examples of alkoxycarbonylalkyl and carboxamidoalkyl groups are: Ethoxycarbonylmethyl, 2-butoxy-carbonylethyl, diethylaminocarbonylmethyl, 2-diethylaminocarbonylethyl, 2-pyrrolidonocarbonylethyl, and piperazinocarbonylmethyl.

The groups R_1, R_2, which are preferably alkyl groups containing 1 to 5 carbon atoms, may also be substituted, more especially terminally, by one or more amino groups, in which the nitrogen may optionally be mono- or di-substituted by alkyl groups containing preferably 1 to 5 carbon atoms or may be a constituent of a 4- to 7-membered ring. Examples of N-substituted alkyl groups are: aminomethyl, 2-methylaminoethyl, 2-dimethylaminoethyl, 2-diethylaminoethyl, 3-dimethylaminopropyl, 3-ethylmethylaminopropyl, pyrrolidino, piperidino, N-methylpiperazino, and hexamethylene-imino.

When R_1 and/or R_2 in the compounds of the general formula I represent cycloalkyl or cycloalkyl-alkyl groups, the latter preferably contain 3 to 7 carbon atoms in the cycloalkyl moiety. Preferred cyclic groups are the cyclopropyl, cyclopropylmethyl, cyclopentyl and cyclohexyl groups.

An aryl or aralkyl group R_1 or R_2 is more especially a phenyl or benzyl group.

Preferred compounds of the general formula I are those in which R_3 represents a methyl group.

As residues R_4 there may be mentioned, apart from hydrogen, alkyl groups containing not more than 5 carbon atoms such as, for example, the methyl and ethyl group, aryl groups, especially the phenyl group, and acyl groups, such as, for example, the acetyl, propionyl, butyryl and pivaloyl groups.

Racemic and optically active compounds of the general formula I are valuable neuropsychotropic medicaments. The compounds generally exhibit central-depressive, apomorphine-antagonistic and anti-nociceptive action and to that extent have a certain similarity to chlorpromazin (literature: Modern Problems of Pharmacopsychiatry, Volume 5, pages 33—44; Janssen P.A.Y., "Chemical and Pharmacological Classification of Neuroleptics", edited by Bobon D.P. et al., S. Karger Verlag Basel, Munchen, Paris, New York (1970)). On the other hand, compounds of the invention differ from chlorpromazin in having less pronounced reflex disturbance, less pronounced sedating and narcotic properties and a different influence on biogenic amines. Thus, for example, 4-(3,4-dimethoxyphenyl)-2-pyrrolidone has a prolonging action on barbitol sleeping time that is about 20 times weaker than that of chlorpromazin.

The new compounds are generally distinguished by the rapid onset of their action and low acute toxicity.

The favourable properties of the compounds of the invention could not be expected, because, as our tests have shown, the corresponding para- and meta-monosubstituted phenyl-2-pyrrolidones have either a different spectrum of action or exhibit only slight action. For example, 4-(4-Chlorophenyl)-2-pyrrolidone, which is described in Japanese Patent 70 16,692, has an anticonvulsive action. Unsubstituted phenyl-2-pyrrolidones are only very weakly active.

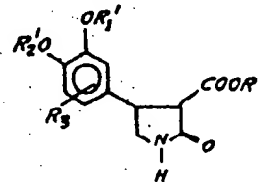
By virtue of the actions described above the compounds of the invention can be used in the form of pharmaceutical preparations for the treatment of various neurological and psychological disturbances, especially as neuroleptics having a reduced extrapyramidal symtomatology. The present invention accordingly also provides a pharmaceutical preparation comprising one or more compounds of the general formula I in admixture or conjunction with a pharmaceutically suitable carrier.

The preparations may be formulated with the carrier substances customarily used for enteral or parenteral administration, such as, for example, water, alcohol, gelatine, gum arabic, lactose, starches, magnesium stearate, talcum, vegetable oils, and polyalkylene glycol. The preparations may be in solid form, for example, as tablets, capsules, drugees, suppositories or in liquid form as solutions, suspensions or emulsions. For oral administration the quantity of active substance per oral unit of administration is advantageously 1—20 mg; preferably 5—10 mg. The daily dose is advantageously 1—50 mg, and preferably 10—30 mg, *per os*.

For parenteral administration the quantity of active substance per unit of administration is advantageously 0.05—10 mg, and preferably 0.1 to 5 mg. The daily dose may be 0.1—20 mg, and preferably 0.2—5 mg, given intravenously or intramuscularly.

The present invention also provides a process for the manufacture of a 4-(alkoxy-phenyl)-2-pyrrolidone of the general formula I in which:

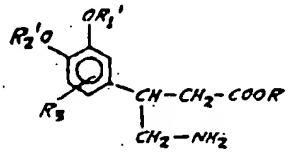
(a) a compound of the general formula II



(II)

in which R_1' and R_1' may be the same or different and each represents a hydrogen atom, or an acyl group or the corresponding group R_1, R_2 as hereinbefore defined,
R_3 is as hereinbefore defined, and
R represents an alkyl group, is hydrolysed and decarboxylated by a method suitable for the purpose; or

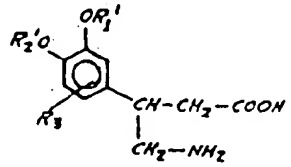
(b) a 3-(substituted phenyl)-4-amino butyric acid ester of the general formula III



(III)

in which R_1', R_1', R_3 and R are as defined at (a) above, or an acid addition salt thereof, is subjected to a suitable ring closure reaction with the elimination of the corresponding alcohol R—OH; or

(c) a 3-(substituted phenyl)-4-aminobutyric acid of the general formula IV



(IV)

in which R_1', R_2' and R_3 are as defined at (a) above, or an acid addition salt thereof, is subjected t a suitable ring-closure reaction with the elimination of water; and the product of reaction (a), (b) or (c), as the case may be, is optionally (i) hydrocarbylated to convert —OR_1' and/or —OR_2' int —OR_1 and/or —OR_2, (ii) alkylated, arylated or acylated at the —NH— group at position 1, (iii) c nverted to the corresponding thione, and/or (iv) subjected to racemic separation.

An alkyl group R is preferably one containing not more than 5 carbon atoms.

Suitable methods for carrying out the foregoing transformations will be well-known to those skilled in the art.

The hydrolysis according to process (a) will generally be carried out with aqueous alkali, advantageously in a solvent miscible with water, for example, in an alcohol such as ethanol, in tetrahydrofurane or dioxane, and is preferably carried out at temperatures between about 60 and 150°C, more especially under boiling conditions. The decarboxylation according to (a) may be carried out by heating the corresponding carboxylic acid at about 160 to 280°C. Preferably, the substance is heated *in vacuo* for this purpose, although the elimination of CO_2 may also be carried out in the presence of a high-boiling inert solvent such as, for example, diphenyl ether or quinoline.

The ring closure according to process (b), involving elimination of an alcohol, will generally be effected in an organic solvent, such, for example, as dimethylformamide, dimethylacetamide, tetrahydrofurane, dioxane, benzene, toluene, or xylene, while heating at about 50 to 150°C. When the starting material is a salt, for example, the hydrochloride, of the amino-acid ester of the general formula III, the heating should be carried out in the presence of a tertiary base. Tertiary bases which may be used include trialkylamines such as, for example, triethylamine and tributylamine, and also, for example, N-methyl-morpholine, diethyl-cyclohexylamine, or pyridine.

In accordance with process (c) the ring closure will generally be carried out with the splitting off of water at a temperature between about 160 and 280°C. It is of advantage to work *in vacuo*, because the water split off can then be more easily removed and the access of atmospheric oxygen is prevented. When the corresponding acid addition salts are used as starting materials, heating should be carried out in the presence of a tertiary base as described above with reference to (b).

When the compound obtained in accordance with (a), (b) or (c), is one in which R_1' or R_2' represents a hydrogen atom, appropriate O-hydrocarbylation will normally be required for subsequent conversion into an end product of the general formula I. Such alkylation, for example, is preferably carried out with the corresponding R_1- or R_2-halide or tosylate in conventional manner. The corresponding chloride, bromide or iodide may be used. To effect alkylation the hydroxy-compound may be dissolved, for example, in a polar solvent, and heated in the presence of a base with the alkylating agent at a temperature between 30 and 150°C. Examples of bases which may be used include sodium hydride, potassium carbonate, and alkali alcoholates such as, for instance, sodium ethylate, potassium butylate and potassium tert.-butylate. As polar solvents there may be mentioned dimethylformamide, dimethylacetamide, tetrahydrofurane, dioxane, ketones such as, for example, acetone and methyl isobutyl ketone, and also alcohols such as, for example, ethanol, butanol and tert.-butanol. Alkylation, arylation or acylation of the imino group may also be carried out by known methods. Thus, for example, the imino-compound (in which R_3=H) is dissolved in a polar solvent and heated in the presence of a salt-former with an alkyl, aryl or acyl halide at about 40 to 150°C. As polar solvent there may be used dimethylformamide, dimethylacetamide, tetrahydrofurane, dioxane, a ketone such as acetone or methyl isobutyl ketone, or an alchol such as ethanol or butanol. Suitable salt-formers include, for example, sodium hydride, potassium carbonate, and alkali alcoholates such as, for instance, sodium ethylate or potassium tert.-butylate. The reaction with a halogen-aryl, for example, iodobenzene, may instead be carried out without a solvent, preferably in the presence of copper powder.

The exchange of carbonyl-oxygen for sulphur may be carried out by methods described in the literature for such compounds (reference is made in this connection to J. W. Scheeren, P. H. J. Ohms, R. J. F. Nivard, Synthesis 1973, 149—151). For this purpose there may be used, for example, a polysulphide such as, for instanc , phosphorus pentasulphide, in a solvent or mixture of solvents and in the presence of a base. The reaction may also be carried out in a suspension system. Suitable solvents or suspension media include, for example, acetonitrile,

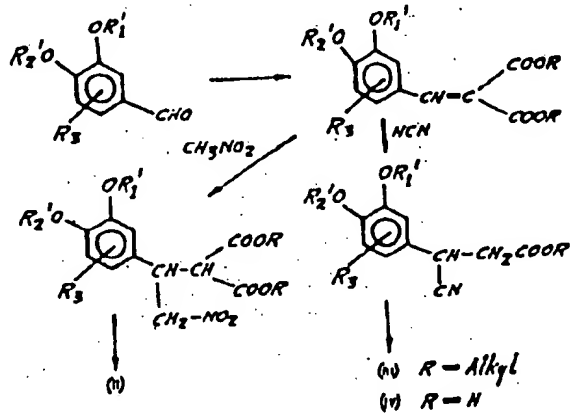
tetrahydrofurane, diethyl ether and glycol dimethyl ether. As base there may be used, for example, sodium hydrogen carbonate or potassium carbonate. At 30 to 120°C the reaction will generally be ov r after 3 to 24 hours.

The starting compounds of the formulae II, III and IV can also be prepared by known methods, for example, in the following manner:

Starting from benzaldehyde substituted by OR_1', OR_2' and R_3, there is prepared, with a malonic acid dialkyl ester, the corresponding benzal-malonic acid dialkyl ester, which can be converted into the corresponding 4-(substituted phenyl)-2-pyrrolidone-3-carboxylic acid alkyl ester of the general formula II by reaction with nitromethane in the presence of trimethyl-guanidine to yield the 1-(substituted phenyl)-2-nitroethyl-malonic acid dialkyl ester followed by hydrogenation under pressure using a Raney nickel catalyst.

For preparing 3-(substituted phenyl)-4-amino-butyric acid alkyl esters of the general formula III HCN is additively combined by means of potassium cyanide at the double bond of the benzal-malonic acid diester in aqueous alcohol while heating at 60°C: there is simultaneous elimination of a carbalkoxy group, and the cyano-compound is hydrogenated under pressure in the presence of platinum dioxide. If the additive combination of HCN is instead carried out under boiling conditions, the corresponding butyric acid of the general formula IV is formed.

The reactions of substituted benzaldehydes to form the compounds II, III and IV are also illustrated with reference to the following scheme of reactions:



The processes are described more fully below.

The working-up procedure adopted in each case comprises extraction with the solvent mentioned, washing the organic phase with saturated sodium chloride solution, drying over anhydrous calcium sulphate and evaporation *in vacuo* at a bath temperature of 40—45°C. Additional treatment of the organic phase, such as washing with acid or alkali, is specially mentioned in the description.

It should be noted that the yields quoted are not necessarily optimum values. No routine optimizing tests were carried out.

All temperatures are quoted in degrees Centigrade (°C) and the pressures quoted in the boiling point data are in mm Hg.

Substances referred to as crude products were tested for sufficient purity by thin-layer chromatography (TLC) in at least two systems and by means of infra-red spectraoscopy. All other substances were analytically pure (C-, H- and N- determinations; IR-, UV- and NMR-spectra; thin-layer chromatogrphy; titrations and gas chromatography in some cases).

After the melting point determined on a Kofler block there is given in parenthesis the solvent used for recrystallisation.

The following abbreviations are used for the solvents:

DMF	Dimethylformamide
EA	Ethyl acetate
DIP	Diisopropyl ether
W	Water
AcOH	Glacial acetic acid
Bzl.	Benzene

Compounds of the general formula II may be prepared, for example, as follows:

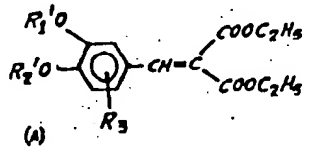
(A) Benzal-malonic acid diethyl ester

1 Mol of a correspondingly substituted benzaldehyde is heated under a water separator with 160 grams of diethyl malonate (1 mol), 30 ml of glacial acetic acid and 3 ml of piperidine in 1 litre of benzene until one mol of water has been eliminated. The benzene solution is worked up in the usual manner.

3-Isobutoxy-4-methoxy-benzaldehyde is prepared as follows:

108 grams of 3-hydroxy-4-methoxy-benzaldehyde (710 mMol) are heated under boiling conditions with 40.5 grams of potassium hydroxide (723 mMol) and 120 grams of isobutyl bromide (875 mMol) in 250 ml of ethanol for 26 hours, while stirring. After distilling off the alcohol *in vacuo*, the residue is worked up in the usual manner with ethyl acetate, but in addition is washed with a 2N-solution of sodium hydroxide. From the alkaline extract there are recovered by acidification 35 grams of the starting material. The yield of 3-isobutoxy-4-methoxy-benzaldehyde is 80 grams. Melting point: 70° (heptane).

In the following Table are summarised the yields and boiling or melting points of several compounds of structure (A):



(A)

	R_1'	R_2'	R_3	Yield (% of theory)	Boiling point, melting point (recrystallisation agent)
a	CH_3	$-CH_3$	-H	70	$Bp_{0.4}$ 185–189°
b	$-CH_2-$		-H	53	$Bp_{0.4}$ 172°
c	$-CH_2CH_2-$		-H	88	Bp_1 227–289°
d	$-CH_2CH(CH_3)_2$	$-CH_3$	-H	95	$Bp_{0.1}$ 190–192°
e	-H	$-CH_3$	-H	78	Bp_1 213–215°C
					Mp. 86° (DIP)
f	$-CH_3$	-H	-H	77	– Mp 121° (DIP)
g	$-CH_3$	$-CH_3$	2-OCH_3	100	Crude product (TLC, IR)
h	$-CH_3$	$-CH_3$	5-OCH_3	75	$Bp_{0.2}$ 180–182°
					Mp. – 70°
i	$-CH_3$	$-CH_3$	6-OCH_3	90	Mp. 100° (DIP)

(B) 1(Substituted phenyl)-2-nitroethyl-malonic acid diethyl ester

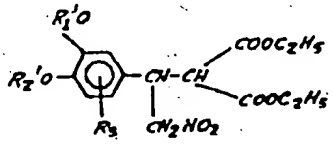
500 mMol of the corresponding benzal-malonic acid diethyl ester (formula A) are dissolved in 250 ml of nitromethane, and 12.7 ml of tetramethyl-guanidine are added at 0°C while stirring. When the exothermic reaction has subsided, the whole is stirred for a further 18 hours at room temperature. The reaction mixture is worked up in the usual manner with ethyl acetate, but is washed in addition with 2N-hydrochloric acid. The acetoxy-methoxy-benzal-malonic esters required for examples B(b) and B(c) are prepared as follows:

150 grams of (3-hydroxy-4-methoxy-benzal)-malonic acid diethyl ester (510 mMol) (see Ae above) are dissolved in 450 ml of pyridine, and 57 ml of acetic anhydride (604 mMol) are added dropwise while cooling with ice. After allowing the mixture to stand for 18 hours at room temperature, the pyridine is removed *in vacuo*. The usual working up with ethyl acetate yields 163 grams of (3-acetoxy-4-methoxy-benzal)-malonic acid diethyl ester (95% of theory) melting at 75—77° (diisopropyl ether).

In an analogous manner (4-hydroxy-3-methoxy-benzal)-malonate (see Af above) is acetylated to form the corresponding 4-acetoxy-3-methoxy-compound. Yield: 95%. Melting point: 51° (diisopropyl ether-petroleum ether).

The Table below summarises yields and boiling or melting points for several compounds of formula (B):

(B)

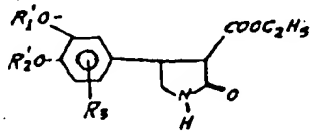


	R_1'	R_2'	R_3	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-CH_3$	$-CH_3$	$-H$	59	75° (Methylene chloride-DIP)
b	$-COCH_3$	$-CH_3$	$-H$	95	Crude product (TLC, IR)
c	$-CH_3$	$-COCH_3$	$-H$	95	Crude product (TLC, IR)
d	$-CH_3$	$-CH_3$	2-OCH_3	65	Chromatography over SiO_2 (Cyclohexane-ethyl acetate 1 : 1 by volume)
e	$-CH_3$	$-CH_3$	6-OCH_3	70	Chromatography over SiO_2 (Cyclohexane-ethyl acetate 1 : 1 by volume)

(C) 4-(Substituted phenyl)-2-pyrrolidone-3-carboxylic acid ethyl ester (II)

300 mMol of the corresponding 1-substituted-phenyl-2-nitroethyl-malonic acid diethyl ester are dissolved in 700 ml of methanol, and hydrogenated using about 10 grams of Raney nickel at 60° and 95 atmospheres pressure until 3 mol of hydrogen have been absorbed. The mixture is then filtered to remove the catalyst, concentrated *in vacuo*, and the oily residue is recrystallised.

The Table below summarises yields and melting points of several compounds of structure (C), which is formula II of process type (a):



	R_1'	R_2'	R_3	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-CH_3$	$-CH_3$	-H	84	106° (EA)
b	-H	$-CH_3$	-H	70	125° (EA–DIP) (Splitting off the acetyl group with hydrogenation and working up.)
c	$-CH_3$	-COOH	-H	62	172° (EA)
d	$-CH_3$	$-CH_3$	2-OCH_3	60	99° (EA–DIP)
e	$-CH_3$	$-CH_3$	6-OCH_3	20	131° (ethanol)

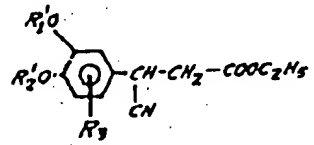
Compounds of the general formula III can be prepared, for example, in the following manner:

(D) 3-(Substituted phenyl)-3-cyano-propionic acid ethyl ester

To 100 mMol of a corresponding benzal-malonic ester (see formula A) in 180 ml of ethanol is added a solution of 6.5 grams of potassium cyanide (100 mMol) in 25 ml of water, and the mixture is heated for 7 hours at 60°C. After allowing the mixture to stand for 18 hours at room temperature, the solvent is removed in vacuo, and the residue is worked up in the usual manner with ethyl acetate but is extracted in addition with a 1N-solution of sodium hydroxide. The corresponding 3-phenyl-3-cyano-propionic acid ester can be obtained from the sodium hydroxide extract solution if necessary by acidification.

The yield and melting or boiling point for several compounds of structure (D) is given below:

(D)



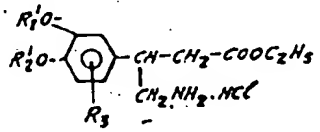
	R_1'	R_2'	R_3	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-CH_3$	$-CH_3$	-H	85	$Bp_{0.1}$ 177–182°
b	$-CH_2-$		-H	82	Crude product (TLC, IR)
c	$-CH_2CH_2-$		-H	84	Crude product (TLC, IR)
d	$-CH_2CH(CH_3)_2$	$-CH_3$	-H	83	Crude product (TLC, IR)
e	$-CH_3$	-H	-H	91	Crude product (TLC, IR)
f	$-CH_3$	$-CH_3$	5-OCH_3	60	Mp. 84° (EtOH)

(E) 3-(Substituted phenyl)-4-amino-butyric acid ethyl ester hydrochloride (III)

50 mMol of 3-phenyl-3-cyano-pr pionic acid ethyl ester (D) are hydrogenated in 60 ml of glacial acetic acid over 1 gram of platinum oxide at room temperature and 100 atmospheres until 2 mol of hydrogen have been absorbed. The catalyst is

then filtered off with suction, and, after the addition of 25 ml of 2N-methanolic hydrochloric acid, the mixture is evaporated to a small volume *in vacuo*. The products of formula (E) may be used as starting materials in process type (b).

(E)



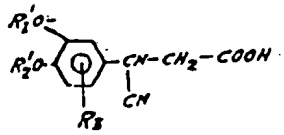
	R_1'	R_2'	R_3	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-CH_3$	$-CH_3$	$-H$	90	M.p. 185° (ACOH)
b	$-CH_2-$		$-H$	79	Crude product (TLC, IR)
c	$-CH_2CH_2-$		$-H$	100	Crude product (TLC, IR)
d	$-CH_2CH(CH_3)_2$	$-CH_3$	$-H$	63	M.p. 124° (EA)
f	$-CH_3$	$-CH_3$	5-OCH_3	100	Crude product (TLC, IR)
g	$-CH_3$	$-H$	$-H$	100	Crude product (TLC, IR)

Compounds of the general formula IV, for use in process type (c), can be prepared as follows:

(F) 3-(Substituted phenyl)-3-cyano-propionic acid

By reacting a correspondingly substituted benzal-malonic ester (see under A) with potassium cyanide in the same relative proportions and for the same reaction times as are described under D, but under boiling conditions, the equivalent 3-(substituted phenyl)-3-cyano-propionic acid is obtained. The latter, after evaporating the solvent, taking up the residue in water, washing with ethyl acetate and acidifying the aqueous phase, is isolated and purified by crystallisation.

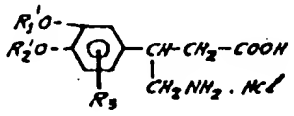
(F)



	R_1'	R_2'	R_3	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-CH_3$	$-CH_3$	$-H$	54	Mp. 133–135° (ethanol)
b	$-CH_2-$		$-H$	63	Crude product (TLC, IR)
c	$-CH_2CH_2-$		$-H$	76	Crude product (TLC, IR)
d	$-CH_3$	$-CH_3$	5-OCH_3	78	Crude product (TLC, IR)

(G) 3-(Substituted phenyl)-4-amino-butyric acid hydrochloride (IV)

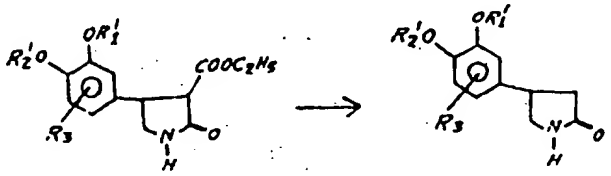
100 mMol of 3-(substituted phenyl)-3-cyano-propionic acid (formula F) are hydrogenated in 200 ml of glacial acetic acid with the addition of 9.5 ml of concentrated hydrochl ric acid over 3 grams of platinum dioxide at r om temperature and 100 atmospheres until 2 mol of hydrogen have been absorbed. The mixture is filtered to remove the catalyst and evaporated *in vacuo*. By crystallisation of the largely oily residue the corresponding 3-(substituted phenyl)-4-amino-butyric acid hydrochloride is obtained.

(G) 

	R_1'	R_2'	R_3	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-CH_3$	$-CH_3$	$-H$	50	Mp. 220° (Decomp.) (AcOH)
b	$-CH_2-$		$-H$	43	Mp. 210° (1N–HCl)
c	$-CH_2CH_2-$		$-H$	52	Mp. 207° (ethanol-DIP)
d	$-CH_3$	$-CH_3$	5-OCH_3	45	Mp. 204° (isopropanol)

The following Examples illustrate the manufacture and utilisation of substituted pyrrolidones according to the invention:

Example 1
4-(Substituted phenyl)-2-pyrrolidones



50 mMol of a 4-(substituted phenyl)-2-pyrrolidone-3-carboxylic acid ethyl ester (prepared for instance according to C above) are heated at the boil for one hour with 200 ml of ethanol and 60 ml of a 1N-solution of sodium hydroxide. After distilling off the solvent *in vacuo*, the residue is taken up in ethyl acetate and extracted with water, optionally with the addition of a little sodium hydroxide solution. From the aqueous phase after saturating with sodium chloride the 4-(substituted phenyl)-2-pyrrolidone-3-carboxylic acid is precipitated by means of 5N-hydrochloric acid. After allowing the mixture to stand in the cold for a short time, the precipitate is filtered off with suction and washed with a small amount of ice-water. Decarboxylation of the pyrrolidone carboxylic acid is carried out by heating it at 200°C *in vacuo* until the evolution of CO_2 ceases. The residue is recrystallised, optionally with the addition of carbon.

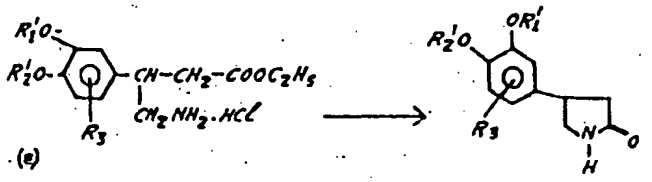
The following Table summarises the yield and melting or boiling point of several substituted pyrrolidones made by this method:

	R_1'	R_2'	R_3	Yield (% of theory)	Boiling point, melting point (recrystallisation agent)
b	-H	$-CH_3$	-H	45	144° (isopropanol)
c	$-CH_3$	-H	-H	40	$Bp_{0.6}$ 230° *
d	$-CH_3$	$-CH_3$	2-OCH_3	57	93° (EA)
e	$-CH_3$	$-CH_3$	6-OCH_3	65	103° (EA)

*Chromatography over silica gel (Bzl.-AcOH—H_2O, 10:10:1 by volume) with simultaneous hydrolysis of the 4-acetoxy groups. (Analogous hydrolysis occurs in making compound I b):

I b) 4-(3-Hydroxy-4-methoxy-phenyl)-2-pyrrolidone.
I c) 4-(4-Hydroxy-3-methoxy-phenyl)-2-pyrrolidone.
I d) 4-(2,3,4-Trimethoxy-phenyl)-2-pyrrolidone.
I e) 4-(3,4,6-Trimethoxy-phenyl)-2-pyrrolidone.

Example 2
4-(Substituted phenyl)-2-pyrrolidones



Process I

10 mMol of a 3-(substituted phenyl)-4-amino-butyric acid ethyl ester hydrochloride are dissolved in 15 ml of dimethylformamide, 1.4 ml of triethylamine (10 mMol) are added, and the whole is heated for 6 hours at 70°C. After evaporation *in vacuo*, working up is carried out in the usual manner with ethyl acetate.

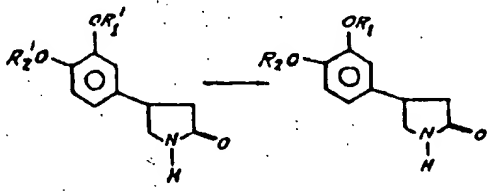
Process II

While stirring, 10 mMol of a 3-(substituted phenyl)-4-amino-butyric acid ethyl ester hydrochloride and 1.4 ml of triethylamine (10 mMol) in 50 ml of benzene are heated at the boil until a negative ninhydrin reaction is obtained, and the mixture is worked up in the usual manner.

	Process	R_1'	R_2'	R_3	Yield (% of theory)	Boiling point, melting point (recrystallisation agent)
b	II	$-CH_2-$		-H	49	Mp. 157° (EA)
c	II	$-CH_2CH_2-$		-H	54	Mp. 104° (EA)
d	II	$-CH_2CH(CH_3)_2$	$-CH_3$	-H	50	Mp. 150° (EA)
e	I	$-CH_3$	-H	-H	10	$Bp_{0.6}$ 230° Chromatography over SiO_2 (Bzl-AcOH-H_2O, 10 : 10 : 1 by volume)

2 b) 4-(3,4-Methylenedioxy-phenyl)-2-pyrrolidone.
2 c) 4-(3,4-Ethylene-dioxy-phenyl)-2-pyrrolidone.
2 d) 4-(3-Isobutoxy-4-methoxy-phenyl)-2-pyrrolidone.
2 e) 4-(4-Hydroxy-3-methoxy-phenyl)-2-pyrrolidone.

Example 3
4-(Alkoxy-methoxy-phenyl)-2-pyrrolidones



Method A

10 mMol of a 4-(Hydroxy-alkoxy-phenyl)-2-pyrrolidone are dissolved in 5 ml of dimethylformamide, 500 mg of a suspension of 50% strength by weight of sodium hydride in paraffin oil (10.5 mMol) are added while cooling with ice, and the whole is slowly heated to 60°C with stirring. When the evolution of hydrogen ceases, 11 mMol of the corresponding R-halide and 100 mg of sodium iodide in 3 ml of dimethylformamide are added at 0°C, and the whole is heated at 100°C for 3 hours, while stirring. The solvent is then distilled off *in vacuo*, and the residue is worked up in the usual manner with ethyl acetate, including in addition an extraction with a 2N-solution of sodium hydroxide.

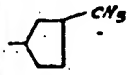
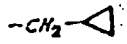
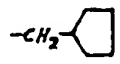
Method B

10 mMol of a 4-(Hydroxy-alkoxy-phenyl)-2-pyrrolidone, 11 mMol of the corresponding halide and 1.45 grams of potassium carbonate (10.5 mMol) are heated at the boil in 30 ml of acetone for 38 hours while stirring. The residue remaining after filtering off the inorganic salts with suction and evaporation *in vacuo*, is worked up as described under method A.

Method C

10 mMol of a 4-(Hydroxy-alkoxy-phenyl)-2-pyrrolidone are dissolved in 22 ml of an 0.5N-solution of sodium butylate in butanol, and heated at the boil with 11 mMol of the corresponding halide for 10 hours while stirring. Working up is carried out as described in method A.

R_2-CH_2	R_1	Method	Yield (% of theory)	Melting point (recrystallisation agent)
a	$-C_2H_5$	C	62	123° (EA)
b	$-C_3H_7$	B	42	124° (EA–DIP)
c	$-C_4H_9$	C	47	125° (DIP)
d	$-C_6H_{13}$	A	48	119° (EA–DIP)
e	$-CH(CH_3)_2$	A	44	123° (EA–DIP)
f	$-CH(CH_3)C_2H_5$	B	41	105° (EA–DIP)
g	$-CH_2-CH(CH_3)_2$	B	40	150° (EA)
h	$-CH_2-CH(CH_3)_2$	B	46	104° (EA–DIP)
i	$-CH_2-CH(CH_3)_3$	B	38	123° (EA–DIP)
k	$-CH_2OCH_3$	A	38	94° (triturated with DIP)
l	$-CH_2-CON(C_2H_5)_2$	A	56	117° (EA-petroleum ether)
m	$-CH_2CH_2OH$	A	34	108° (EA)
n	$-CH_2CF_3$	B	36	110° (EA)
o	$-CH_2-C_6H_5$	A	57	132° (EA)
p	$-C_6H_5$	K_2CO_3, $I-C_6H_5$, DMF, 30 mins., 130°	71	132° (EA)

R_2-CH_3	R_1	Method	Yield (% of theory)	Melting point (recrystallisation agent)
a'	$-C_{10}H_{21}$	A	49	117° (EA)
b'	$-C_{18}H_{37}$	A	40	119° (EA)
c'	$-CH_2-CH(CH_3)(C_2H_5)$	A	50	140° (EA)
d'	$-CH_2-C(CH_3)_2(CH_3)$	A	21	166° (EA–DIP)
e'	$-CH_2-CH_2-CH(CH_3)_2$	A	61	139° (EA)
f'	$-CH_2-C\equiv CH$	A*)	60	116° (EA–DIP)
g'	$-CH_2-C\equiv N$	A	48	144° (EA–DIP)
h'		A	20	140° (EA–DIP)
i'		A*)	30	132° (EA)
k'		A	20	128° (EA–DIP)
l'		A**)	22	128° (EA–DIP)
m'		A**)	19	120° (EA–DIP)
n'		A**)	12	128° ***)
o'		A**)	20	107° ***)
p'		A	50	123° (EA)
q'		A**)	36	132° (EA-hexane)
r'		A	32	173–176° (ethanol)
s'	$-CH_2-C(CH_3)_3$	B	63	130° (EA–DIP)

*) Use of hexamethyl-phosphoric acid triamide instead of DMF
**) Instead of the R-halide the tosylate was used.
***) Chromatography over SiO_2, CH_2Cl_2-acetone (1:1 by volume)

R_1-CH_3	R_2	Method	Yield (% of theory)	Melting point (recrystallisation agent)
q	$-C_2H_5$	C	47	168° (EA)
r	$-C_4H_9$	C	62	118° (DIP)
s	$-CH_2-CON(C_2H_5)_2$	A	53	95° (EA)
t'	$-CH_2-C\equiv CH$	A*)	61	126° (EA)
u'		A*)	62	104° (EA)

R_1-R_2	R_2	Method Method	Yield (% of theory)	Melting point (recrystallisation agent)
v'	$-C_2H_5$	A +)	83	146–148° (EA–DIP)
w'	$-CH_2-CH(CH_3)_2$	A +)	42	88° (hexane)

*) Use of hexamethyl-phosphoric acid triamide instead of DMF.

+) Method A, but with 4-(3,4-dihydroxy-phenyl)-2-pyrrolidone as starting material.

4 a) 4-(3-Ethoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 b) 4-(3-Propoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 c) 4-(3-Butoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 d) 4-(3-Hexyloxy-4-methoxy-phenyl)-2-pyrrolidone.
4 e) 4-(3-Isopropoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 f) 4-(3-[1-Methyl-propoxy]-4-methoxy-phenyl)-2-pyrrolidone.
4 g) 4-(3-Isobutoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 h) 4-(3-Allyloxy-4-methoxy-phenyl)-2-pyrrolidone.
4 i) 4-(3-[3-Methyl-2-butenyloxyl-4-methoxy-phenyl)-2-pyrrolidone.
4 k) 4-(3-Methoxymethoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 l) 4-(3-Diethylaminocarbonylmethoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 m) 4-(3-[2-Hydroxyethoxyl-4-methoxy-phenyl)-2-pyrrolidone.
4 n) 4-(3-[2,2,2-Trifluorethoxyl-4-methoxy-phenyl)-2-pyrrolidone.
4 o) 4-(3-Benzyloxy-4-methoxy-phenyl)-2-pyrrolidone.
4 p) 4-(3-Phenoxy-4-methoxy-phenyl)-2-pyrrolidone.
4 q) 4-(3-Methoxy-4-ethoxy-phenyl)-2-pyrrolidone.
4 r) 4-(3-Methoxy-4-butoxy-phenyl)-2-pyrrolidone.
4 s) 4-(3-Methoxy-4-diethylaminocarbonylmethoxy-phenyl)-2-pyrrolidone.

4 a') 4-(3-Decyloxy-4-methoxyphenyl)-2-pyrrolidone.
b' 4-(3-Octadecyloxy-4-methoxyphenyl)-2-pyrrolidone.
c' 4-(3-(2-Methylbutyl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
d' 4-(3-Neopentyloxy-4-methoxyphenyl)-2-pyrrolid ne.
e' 4-(3-Isopentyloxy-4-methoxyphenyl)-2-pyrrolidone.
f' 4-(3-(2-Propinyl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
g' 4-(3-Cyanomethyloxy-4-methoxyphenyl)-2-pyrrolidone.
h' 4-(3-Cyclobutyloxy-4-methoxyphenyl)-2-pyrrolidone.
i' 4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone.

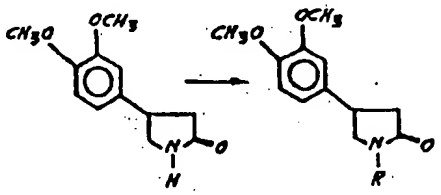
k' 4-(3-Cyclohexyloxy-4-methoxyphenyl)-2-pyrrolidone.
l' 4-(3-(3-Methylcyclopentyl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
m' 4-(3-(2-Methylcyclopentyl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
n' 4-(3-Tetrahydrothienyl)-4-methoxyphenyl)-2-pyrrolid ne.
o' 4-(3-(3-Tetrahydrofuryl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
p' 4-(3-Cyclopropylmethyloxy-4-methoxyphenyl)-2-pyrrolidone.
q' 4-(3-Cyclopentylmethyloxy-4-methoxyphenyl)-2-pyrrolidone.
r' 4-(3-(2-Oxa-cyclopentyloxyl-4-methoxy-phenyl)-2-pyrrolidone.
s' 4-(3-Methallyloxy-4-methoxy-phenyl)-2-pyrrolidone.
t' 4-(4-Propinyloxy-3-methoxy-phenyl)-2-pyrrolidone.
u' 4-(4-Cyclopentyloxy-3-methoxy-phenyl)-2-pyrrolidone.
v' 4-(3,4-Di-ethoxy-phenyl)-2-pyrrolidone.
w' 4-(3,4-Di-isobutoxy-phenyl)-2-pyrrolidone.

The starting material for the preparation of compounds 4 v' and 4 w' (4-(3,4-dihydroxy-phenyll-2-pyrrolidone) may be prepared in the following manner.

4.75 grams of 4-(3,4-dimethoxy-phenyl)-2-pyrrolidone (20 mMol) are dissolved in 130 ml of methylene chloride and there are added at –80°C, dropwise, while stirring and excluding moisture, 11.0 grams of boron tribromide (44 mMol) dissolved in 40 ml of methylene chloride. The whole is allowed to heat up to room temperature overnight, poured into water, and the crystalline precipitate is filtered off with suction. The aqueous phase, after being saturated with sodium chloride, is extracted with ethyl acetate. The ethyl acetate extract is evaporated, and the residue together with the crystalline precipitate is recrystallised from water. There are obtained 3.35 grams of 4-(3,4-dihydroxy-phenyl)-2-pyrrolidone melting at 209—215°C.

Example 4

1-Substituted-4-(3,4-dimethoxy-phenyl)-2-pyrrolidones



R = —CH$_3$, —COCH$_3$,

(a) *4-(3,4-Dimethoxy-phenyl)-1-methyl-2-pyrrolidone*

2.21 grams of 4-(3,4-Dimethoxy-phenyl)-2-pyrrolidone (10 mMol) are dissolved in 15 ml of dimethylformamide, 530 mg of a suspension of 50% strength by weight of sodium hydride in paraffin (11 mMol) are added while cooling with ice, and the whole is slowly heated to 60°C while stirring. When the evolution of hydrogen has ceased, 1.56 grams of methyl iodide (11 mMol) in 5 ml of dimethylformamide are added dropwise at 0°C, and the mixture is heated for 15 minutes at 50°C. The mixture is then poured into water, and worked up with ethyl acetate in the usual manner.

Yield: 1.3 grams of 4-(3,4-dimethoxy-phenyl)-1-methyl-2-pyrrolidone (55% of theory).

Melting point: 69°C (diisopropyl ether).

(b) *1-Acetyl-4-(3,4-dimethoxy-phenyl)-2-pyrrolidone*

With the use of 0.86 gram of acetyl chloride (11 mMol), instead of methyl iodide, there is obtained in a manner analogous to that under (a) 1-acetyl-4-(3,4-dimethoxy-phenyl)-2-pyrrolidone.

Yield: 1.4 grams (53% of theory).

Melting point: 135°C (ethanol).

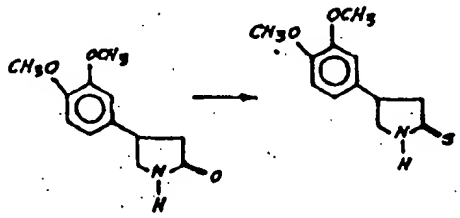
(c) *4-(3,4-Dimethoxy-phenyl)-1-phenyl-2-pyrrolidone*

2.21 grams of 4-(3,4-Dimethoxy-phenyl)-2-pyrrolid ne (10 mMol), 3.5 grams of iodobenzene (17 mMol), 1.44 grams of potassium carbonate (10.4 mMol) and

100 mg of copper powder are heated for 2 hours at 180°C. The usual working up with ethyl acetate yields 2.2 grams of 4-(3,4-dimethoxy-phenyl)-1-phenyl-2-pyrrolidone (74% of theory).
Melting point: 104°C (ethyl acetate/diisopropyl ether).

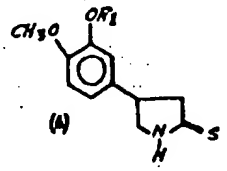
(d) *4-(3,4-Dimethoxy-phenyl)-2-pyrrolidone-1-acetamide*
In a manner analogous to that in 4 (a), but in 5 ml of hexamethyl-phosphoric acid triamide as solvent, the sodium salt of 4-(3,4-dimethoxy-phenyl)-2-pyrrolidone is prepared, 0.94 grams of chloracetamide (10 mMol) are added at 0°, and the whole is heated for 4 hours at 70—90°C, cooled, diluted with water, and worked up in the usual manner with ethyl acetate, including in addition an extraction with a 2N-solution of sodium hydroxide.
Yield: 0.64 gram (23% of theory).
Melting point: 162° (ethanol/DIP).

Example 5
4-(3,4-Dimethoxy-phenyl)-pyrrolidone-2-thione



1.98 grams of 4-(3,4-Dimethoxy-phenyl)-2-pyrrolidone (9 mMol) and 5.4 grams of phosphorus pentasulphide (5.4 mMol) are suspended in a mixture of 9 ml of acetonitrile and 9 ml of glycol dimethyl ether. At room temperature, while stirring, 1.4 grams of sodium hydrogen carbonate (18 mMol) are added in small portions. During further stirring for 1½ hours the suspended material first passes into solution, and the desired 4-(3,4-dimethoxy-phenyl)-pyrrolidone-2-thione crystallises out shortly afterwards. The whole is poured into ice-water and filtered with suction.
Yield: 1.57 grams (78% of theory).
Melting point: 151—152°C (ethanol).

In an analogous manner
4-(3-isobutoxy-4-methoxy-phenyl)-pyrrolidine-2-thione (5 a)
and
4-(3-cyclopentyloxy-4-methoxy-phenyl)-pyrrolidine-2-thione (5 b)
are prepared.



	R_1	Yield (% of theory)	Melting point (Recrystallisation agent)
5a	$-CH_2-CH(CH_3)_2$	68	102—104° (ethanol/W)
5b		42	109—111° (ethanol/W)

Example 6

5 mg of 4-(3-cyclopentyloxy-4-methoxy-phenyl)-2-pyrrolidone
105 mg of lactose
8 mg of maize starch
0.5 mg of magnesium stearate
0.5 mg of Aerosil (Trade Mark)
1.0 mg of talcum

120.0 mg

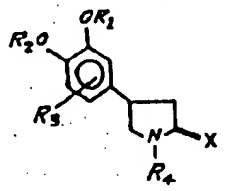
are homogeneously mixed together, and pressed without previous granulation to form tablets having a final weight of 120 mg.

Example 7

5 mg of 4-(3-isobutoxy-4-methoxy-phenyl)-2-pyrrolidone are dissolved in 2 ml of castor oil/benzyl benzoate (4:6 by volume) to produce an oily solution suitable for injection purposes.

WHAT WE CLAIM IS:—

1. A 4-(alkoxy-phenyl)-2-pyrrolidone of the general formula I:



(I)

in which the groups represented by R_1 and R_2 may be the same or different (except that, when R_4 represents a hydrogen atom and X represents an oxygen atom and R_3 represents a group other than a 2-methoxy or 6-methoxy group, at least one of R_1 and R_2 represents a group other than a methyl group) and each is a hydrocarbon group which may be unsubstituted or substituted by one or more halogen atoms, hydroxyl groups, cyano groups, carboxyl groups, alkoxy groups, alkoxycarbonyl, carboxamido or substituted or unsubstituted amino groups, or may be a heterocyclic group containing oxygen or sulphur in the ring, or one of R_1, R_2 represents a hydrogen atom and the other represents a hydrocarbon group as specified above, or R_1 and R_2 together represent an alkylene group containing 1 to 3 carbon atoms; R_3 represents a hydrogen atom or a methoxy group; R_4 represents a hydrogen atom or an alkyl, aryl, acyl or carboxamido group; and X represents an oxygen or sulphur atom.

2. 4-(2,3,4-Trimethoxy-phenyl)-2-pyrrolidone.
3. 4-(3,4,6-Trimethoxy-phenyl)-2-pyrrolidone.
4. 4-(3,4-Methylene-dioxy-phenyl)-2-pyrrolidone.
5. 4-(3,4-Ethylene-dioxy-phenyl)-2-pyrrolidone.
6. 4-(3-Isobutoxy-4-methoxy-phenyl)-2-pyrrolidone.
7. 4-(3-Ethoxy-4-methoxy-phenyl)-2-pyrrolidone.
8. 4-(3-Propoxy-4-methoxy-phenyl)-2-pyrrolidone.
9. 4-(3-Butoxy-4-methoxy-phenyl)-2-pyrrolidone.
10. 4-(3-Hexyloxy-4-methoxy-phenyl)-2-pyrrolidone.
11. 4-(3-Isopropoxy-4-methoxy-phenyl)-2-pyrrolidone.
12. 4-(3-[1-Methyl-propoxy]-4-methoxy-phenyl)-2-pyrrolidone.
13. 4-(3-Isobutoxy-4-methoxy-phenyl)-2-pyrrolidone.
14. 4-(3-Allyloxy-4-methoxy-phenyl)-2-pyrrolidone.
15. 4-(3-[3-Methyl-2-butenyloxy]-4-methoxy-phenyl)-2-pyrrolidone.
16. 4-(3-Methoxymethoxy-4-methoxy-phenyl)-2-pyrrolidone.
17. 4-(3-Diethylaminocarbonylmethoxy-4-methoxy-phenyl)-2-pyrrolidone.
18. 4-(3-[2-Hydroxyethoxy]-4-methoxy-phenyl)-2-pyrrolidone.
19. 4-(3-[2,2,2-Trifluoroethoxy]-4-methoxy-phenyl)-2-pyrrolidone.
20. 4-(3-Benzyloxy-4-methoxy-phenyl)-2-pyrrolidone.
21. 4-(3-Phenoxy-4-methoxy-phenyl)-2-pyrrolidone.
22. 4-(3-Methoxy-4-ethoxy-phenyl)-2-pyrrolidone.
23. 4-(3-Methoxy-4-butoxy-phenyl)-2-pyrrolidone.

24. 4-(3-Methoxy-4-diethylaminocarbonylmethoxy-phenyl)-2-pyrrolidone.
25. 4-(3,4-Dimethoxy-phenyl)-1-methyl-2-pyrrolidone.
26. 1-Acetyl-4-(3,4-dimethoxy-phenyl)-2-pyrrolidone.
27. 4-(3,4-Dimethoxy-phenyl)-1-phenyl-2-pyrrolidone.
28. 4-(3,4-Dimethoxy-phenyl)-pyrrolidone-2-thione.
29. 4-(3-Decyloxy-4-methoxyphenyl)-2-pyrrolidone.
30. 4-(3-Octadecyloxy-4-methoxyphenyl)-2-pyrrolidone.
31. 4-[3-(2-Methylbutyl)-oxy-4-methoxyphenyll)-2-pyrrolidone.
32. 4-(3-Neopentyloxy-4-methoxyphenyl)-2-pyrrolidone.
33. 4-(3-Isopentyloxy-4-methoxyphenyl)-2-pyrrolidone.
34. 4-(3-[2-Propinyll-oxy-4-methoxyphenyl)-2-pyrrolidone.
35. 4-(3-Cyanomethyloxy-4-methoxyphenyl)-2-pyrrolidone.
36. 4-(3-Cyclobutyloxy-4-methoxyphenyl)-2-pyrrolidone.
37. 4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone.
38. 4-(3-Cyclohexyloxy-4-methoxyphenyl)-2-pyrrolidone.
39. 4-(3-(3-Methylcyclopentyl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
40. 4-(3-(2-Methylcyclopentyl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
41. 4-(3-Tetrahydrothienyl)-4-methoxyphenyl)-2-pyrrolidone.
42. 4-(3-(3-Tetrahydrofuryl)-oxy-4-methoxyphenyl)-2-pyrrolidone.
43. 4-(3-Cyclopropylmethyloxy-4-methoxyphenyl)-2-pyrrolidone.
44. 4-(3-Cyclopentylmethyloxy-4-methoxyphenyl)-2-pyrrolidone.
45. 4-(3-[2-Oxa-cyclopentyloxyl-4-methoxy-phenyl)-2-pyrrolidone.
46. 4-(3-Methallyloxy-4-methoxy-phenyl)-2-pyrrolidone.
47. 4-(4-Propinyloxy-3-methoxy-phenyl)-2-pyrrolidone.
48. 4-(4-Cyclopentyloxy-3-methoxy-phenyl)-2-pyrrolidone.
49. 4-(3,4-Di-ethoxy-phenyl)-2-pyrrolidone.
50. 4-(3,4-Di-isobutoxy-phenyl)-2-pyrrolidone.
51. 4-(3-isobutoxy-4-methoxy-phenyl)-pyrrolidone-2-thione.
52. 4-(3-cyclopentyloxy-4-methoxy-phenyl)-pyrrolidone-2-thione.
53. 4-(3,4-Dimethoxy-phenyl)-2-pyrrolidone-1-acetamide.
54. 4-(3-Hydroxy-4-methoxy-phenyl)-2-pyrrolidone.
55. 4-(4-Hydroxy-3-methoxy-phenyl)-2-pyrrolidone.

56. A compound as claimed in claim 1, in which each of R_1 and R_2 represents a hydrocarbon radical as specified.

57. A compound as claimed in claim 1 or claim 56, in which R_4 represents a hydrogen atom or an alkyl, aryl or acyl group.

58. A compound as claimed in any one of claims 1, 56 or 57, in which neither of the groups represented by R_1 and R_2 contains more than 18 carbon atoms.

59. A compound as claimed in any one of claims 1, 56—58, in which one or each of R_1 and R_2 represents a substituted or unsubstituted alkyl group containing from 1 to 5 carbon atoms.

60. A compound as claimed in any one of claims 1, 56—59, in which R_2 represents a methyl group.

61. A compound as claimed in any one of claims 1, 56—59, in which one or each of R_1 and R_2 represents a cycloalkyl or cycloalkyl-alkyl group.

62. A compound as claimed in claim 61, wherein the or each cycloalkyl or cycloalkyl-alkyl group contains from 3 to 7 carbon atoms in the cycloalkyl moiety.

63. A compound as claimed in any one of claims 1, 56—58, in which one or each of R_1 and R_2 represents an aryl or aralkyl group.

64. A compound as claimed in claim 63, in which the or each aryl or aralkyl group contains from 6 to 10 carbon atoms.

65. A compound as claimed in claim 64, in which the or each aryl or aralkyl group is a phenyl or benzyl group.

66. A compound as claimed in any one of claims 1, 56—65, in which a halogen substituent in the group represented by R_1 and/or R_2 is a fluorine, chlorine or bromine atom.

67. A compound as claimed in any of claims 1, 56—65, in which an alkoxycarbonyl substituent in R_1 and/or R_2 contains nore more than 5 carbon atoms in the alkoxy component.

68. A compound as claimed in any one of claims 1, 56—65, in which a carboxy amido substituent in R_1 and/or R_2 contains nitrogen which is mono- or di-substituted by alkyl containing 1 to 5 carbon atoms.

69. A compound as claimed in any one of claims 1, 56—65, in which a carboxy amide substituent in R_1 and/opr R_2 contains nitrogen which is a constituent of a 4- to 7-membered ring.

70. A compound as claimed in any one of claims 1, 56—65, in which an amino substituent in R_1 and/or R_2 is unsubstituted or is substituted by one or more alkyl groups containing 1 to 5 carbon atoms or is a constituent of a 4- to 7-membered ring.

71. A compound as claimed in any one of claims 1, 66—70, wherein a substituent in R_1 and/or R_2 is a terminal substituent.

72. A compound as claimed in any one of claims 1, 56—71, wherein an alkyl group R_4 comprises an alkyl group containing not more than 5 carbon atoms.

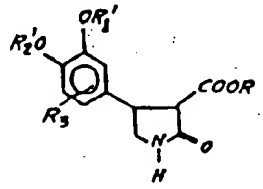
73. A compound as claimed in claim 72, wherein an alkyl group R_4 comprises a methyl or ethyl group.

74. A compound as claimed in any one of claims 1, 56—71, wherein an aryl group R_4 comprises a phenyl group.

75. A compound as claimed in any one of claims 1, 56—74, wherein X represents an oxygen atom.

76. A process for the manufacture of a 4-(alkoxy-phenyl)-2-pyrrolidone of the general formula I defined in claim 1, in which:

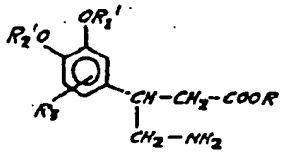
(a) a compound of the general formula II



(II)

in which R_1' and R_2' may be the same or different and each represents a hydrogen atom, or an acyl group or the corresponding group R_1, R_2 as defined in claim 1, R_3 is as defined in claim 1, and
R represents an alkyl group, is hydrolysed and decarboxylated by a method suitable for the purpuse; or

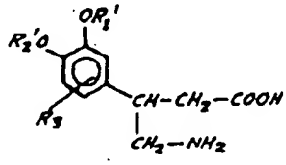
(b) a 3-(substituted phenyl)-4-amino butyric acid ester of the general formula III



(III)

in which R_1', R_2', R_3 and R are as defined at (a) above, or an acid addition salt thereof, is subjected to a suitable ring closure reaction with the elimination of the corresponding alcohol R—OH; or

(c) a 3-(substituted phenyl)-4-aminobutyric acid of the general formula IV



(IV)

in which R_1', R_2' and R_3 are as defined at (a) above, or an acid addition salt thereof, is subjected to a suitable ring-closure reaction with the elimination of water; and the product of reaction (a), (b) or (c), as the case may be, is optionally (i) hydrocarbylated to convert $—OR_1'$ and/or $—OR_2'$ into $—OR_1$ and/or $—OR_2$, (ii) alkylated, arylated or acylated at the —NH— group at position 1, (iii) converted to the corresponding thione, and/or (iv) subjected to racemic separation.

77. A process as claimed in claim 76, wherein an alkyl group R is an alkyl group containing not more than 5 carbon atoms.

78. A process as claimed in claim 76 or 77, wherein a hydrolysis of a compound of the general formula II is effected with aqueous alkali.

79. A process as claimed in any one of claims 76 to 78, wherein a hydrolysis in operation (a) is effected in a water-miscible solvent.

80. A process as claimed in any one of claims 76 to 79, wherein a hydrolysis in operation (a) is effected at a temperature in the range of from 60° to 150°C.

81. A process as claimed in claim 80, wherein said hydrolysis is effected under boiling conditions.

82. A process as claimed in any one of claims 76 to 81, wherein a decarboxylation in operation (a) is effected by heating the corresponding carboxylic acid to a temperature in the range of from 160° to 280°C.

83. A process as claimed in claim 82, wherein said heating is effected *in vacuo*.

84. A process as claimed in claim 76, wherein a ring-closure in operation (b) is effected by heating the compound III in an organic solvent at a temperature in the range of from 50° to 150°C.

85. A process as claimed in claim 76, wherein a ring-closure in operation (c) is effected by heating the compound IV to a temperature in the range of from 160° to 280°C.

86. A process as claimed in claim 85, wherein said ring-closure is effected *in vacuo*.

87. A process for the manufacture of a compound as defined in claim 1, conducted substantially as described in any one of Examples 1 to 5 herein.

88. A compound of the general formula I as defined in claim 1, whenever prepared by a process as claimed in any one of claims 76 to 87.

89. A compound as claimed in claim 88 or in any one of claims 1 to 75, in the form of a racemate.

90. A compound as claimed in claim 88 or in any one of claims 1 to 75, in optically active form.

91. A pharmaceutical preparation comprising one or more compounds as claimed in any one of claims 1 to 75 or 88 to 90, in admixture or conjunction with a pharmaceutically suitable carrier.

92. A pharmaceutical preparation as claimed in claim 91, in the form of tablets, capsules, dragees, or suppositories, or in solution, suspension or emulsion form.

93. A pharmaceutical preparation as claimed in claim 91 or claim 92, which is in a form suitable for oral administration.

94. A pharmaceutical preparation as claimed in claim 93, which is in unit dosage form and in which total quantity of said compound(s) is in the range of from 1 to 20 mg per unit.

95. A pharmaceutical preparation as claimed in claim 94, wherein said total quantity is in the range of from 5 to 10 mg per unit.

96. A pharmaceutical preparation as claimed in claim 91 or claim 92, which is in a form suitable for parenteral administration.

97. A pharmaceutical preparation as claimed in claim 96, which is in unit dosage form and in which the total quantity of said compound(s) per unit is in the range of from 0.05 to 10 mg.

98. A pharmaceutical preparation as claimed in claim 97, wherein said total quantity is in the range of from 0.1 to 5 mg per unit.

99. A pharmaceutical preparation substantially as described in Example 6 or Example 7 herein.

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